

D+ Radiation  
cigarette smoking  
polonium

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Dr. Edward A. Martell  
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Dear Dr. Martell,

This is to respond to your letter of January 2nd concerning the role of radiation in "spontaneous" mutagenesis. I do not know of any analyses that are directed to the specific question that you raise. They could only be answered satisfactorily with the help of experimental information on the dose-response figures for ~~polonium~~ and  $Pb^{210}$ . It should not be too difficult to obtain such information experimentally along the lines of the scenario that you present. As you point out, Muller and other people who have quoted him since used a more diffuse and essentially ~~linear~~ model for environmental radiation. The best source for critical discussion of the points you raised would probably be Dr. Howard Newcombe, ~~radiology~~ and Health Physics Division, Atomic Energy of Canada Limited, Chalk River, Ontario, Canada.

My own experimental work has much more to do with bacteria and viruses and I would be rather skeptical about the role of particular sources for the single base-substitution mutants that are frequently found in these simple forms. It would be rather difficult to account for the very high degree of locus, even site-specificity on the basis of an external radiation model and there is already a more than sufficient explanation in terms of errors in DNA replication. In fact, one can obtain mutations effecting the integrity of the DNA polymerase that are expressed in terms of varying rates of mutation and it is therefore difficult to believe that the initial "wild type" does not simply represent a lower rate of the same process which is exaggerated in some of the mutants.

However, I am not sure to what extent we can always extrapolate from these kinds of observations to the process of mutation in eukaryotes and your question should certainly be addressed at an empirical level.

As to your second question, this is of course a completely controversial subject, even to the question ~~whether~~ malignant change is based on somatic cell mutation as we customarily view it. Only very recently are we in a position to make any experimental analysis of this point, principally by the techniques of somatic cell hybridization that Henry Harris has pioneered. And I would simply suggest that you look up his numerous publications or write to him at the Department of Pathology, Oxford. Professor George Klein at the Karolinska Institute, Stockholm, has made a strong case for a progressive model of malignant change in which the initial event - which may

over

be a somatic cell mutation or a virus infection - is followed by progressive selection of more deepseated changes resulting finally in a wide variety of structural changes which are commonly seen in a variety of forms of malignancy. Some types of leukemia, for example, are commonly associated with rather specific chromosomal-structural changes but this does not mean that the latter reflects the initial event. And of course you are aware that there may be a very large scale reconstruction of the entire karyotype leading to unbalanced chromosome configurations.

I believe the possibility of polonium as an element of the role of tobacco smoke in lung cancer has been discussed for many years, and in my view entirely credible. I would be inclined to give still higher weight to the role of chemical carcinogens in most circumstances of environmental cancer although I would hardly wish to minimize the possibility of significant interactions among them, or a primary role of radioactive sources in certain special circumstances (even possibly lung cancer) and perhaps viruses as well in particular circumstances. One point to keep in mind about the effects of tobacco is the rather clear evidence that smoking is also associated with a substantial rise in bladder cancer - which is notoriously ~~responsive~~ to chemical carcinogens although even in this case I suppose one could not immediately rule out a radioactive emitter as an ideological agent also.

My own scientific work is really not in this immediate area although I do have a few incidental comments which I will enclose.

Sincerely yours,

Joshua Lederberg  
Professor of Genetics

JL/rr  
Enclosure